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AFFYMETRIX, INC
ATTN: CHIEF IP COUNSEL, LEGAL DEPT.
3380 CENTRAL EXPRESSWAY
SANTA CLARA, CA 95051

EXAMINER	
SPIEGLER, ALEXANDER H	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 03/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/734,752	WARRINGTON ET AL.	
	Examiner	Art Unit	
	Alexander H. Spiegler	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2 and 4-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2 and 4-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 29, 2003 has been entered.

Status of the Application

2. This action is in response to Applicants' preliminary amendment submitted on January 26, 2004. Accordingly, Claims 2 and 4-6 are currently pending and are rejected herein. It is also noted the amendments to the specification filed with Applicants' after-final amendment of July 28, 2003 have not been entered. Any objections or rejections not reiterated are hereby withdrawn.

Priority

3. The following findings of priority have been established:

Provisional Application No. 60/193,179, filed on 3/31/2000, teaches gene expression of genes during the proliferative and secretory phases of the menstrual cycle (in normal patients), and differential expression data comparing normal and malignant gene expression in a number of genes. However, this provisional does not refer to or define "menstrual states", "reproductive states", "reproductive statuses", "markers of different reproductive states", expression profiles of "physiological disorders", expression profiles of "reproductive status", expression profiles of "reproductive state", or the diagnosis of "physiological disorders".

Provisional Application No. 60/231,367, filed on 9/08/2000 appears to be the same specification as that of the instant non-provisional application.

Accordingly, the instant claims have been granted priority to Provisional Application No. 60/231,367, filed on 9/08/2000.

Claim Rejections - 35 USC § 112, 2nd Paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 2 and 4-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 2 over "reference samples of known disease state that are matched to said experimental sample in reproductive state" because it is not clear as to how the reference samples are "matched". The claims suggest the samples are matched by "reproductive state", wherein the reproductive state is determined by determining the "menstrual state" of the individual. However it is uncertain as to what encompasses or is meant by "menstrual state" and how one determines the "menstrual state" of the individual. Furthermore, it is noted, the recitations of "menstrual state" nor "reproductive state" are not defined in the specification.

The specification does state:

> The parameters that are considered in determining physiological state include, but are not limited to age, gender, ethnic origin and reproductive state, which includes, but is not limited to menstrual state, post-partum, pregnancy, lactation and nulliparity"

(page 5).

Given this description, it is not clear as to what is meant by "reproductive state" or "menstrual state". Applicants have only listed possible parameters (and explicitly a non-exhaustive list of parameters) that might be considered to fall under the umbrella of "reproductive state" or "menstrual state". This partial list does apprise one of ordinary skill in the art of the scope of "reproductive state" or "menstrual state", and the metes and bounds of these recitations are unclear. Accordingly, because it is not specifically clear how the reference sample and experimental sample are "matched" in reproductive state, the Claim is indefinite.

Furthermore, the recitation of "the expression profile" lacks antecedent basis, since the claim does not refer to an "expression profile" prior to this recitation.

B) Claim 4 over "matched" and "menstrual state" because it is not clear as to what is meant by the term "matched", how "menstrual states" can be matched, what is encompassed or meant by "menstrual state", or how one determines the "menstrual state" of the individual.

C) Claims 4-5 over "similar" because it is not clear as to what degree of similarity is required for determining whether the experimental sample can be diagnosed with the physiological disorder (or can be used to identify reproductive status). Accordingly, because it is unclear from the specification what applicant intended to cover by the recitation of "similar", this recitation is indefinite.

D) Claims 5-6 over "reproductive status", "reproductive state" and "menstrual state" because it is unclear as to what are meant by these recitations. These recitations are not defined in the specification, nor do the claims or specification apprise one of ordinary skill in the art of their scope (see above discussion of "reproductive state" and "menstrual state"). Furthermore, the recitation of "said sample of unknown origin" lacks antecedent basis, since the claim does

not refer to a sample "of unknown origin" prior to this recitation. Furthermore, in Claim 5, "the reproductive status" and "the experimental sample" lack antecedent basis, since the claim does not refer to "reproductive status" or "experimental sample" prior to this recitation.

E) Claim 6 because it is not clear that there is a correlation or relationship between the differential expression of at least one gene and different reproductive states. For example, if a gene is differentially expressed when comparing two women who are both undergoing menopause (which might be considered to be a "reproductive state" or "menstrual state") it is not clear as to how this gene is a marker of different reproductive states. Presumably, there will be at least some genes that would be differentially expressed between women who have the same "menstrual state" or "reproductive state". Accordingly, because there does not appear to be a clear correlation or relationship between the differential expression of at least one gene and different reproductive states, the claim is indefinite.

Claim Rejections - 35 USC § 112, 1st paragraph - Enablement

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 2 and 4-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of detecting expression of specific genes in the proliferative and secretory endometrium, and methods of detecting expression of specific genes in the endometrial cancers of adenocarcinoma and clear cell carcinoma, does not reasonably

provide enablement for diagnosing *any* disease in a female subject using *any* experimental sample derived from said subject, a method to diagnose *any* physiological disorders in a female, a method to identify *any* reproductive status of a sample derived from a female, or a method to identify *any* markers of different reproductive states in women. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

MPEP 2164.01 states:

> Even though the statute does not use the term 'undue experimentation,' it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)

The *Wands* court outlined several factors to be considered in determining whether a disclosure would require undue experimentation. These factors include, but are not limited to:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Id. at 1404.

In the instant case, the specification does not enable one of skill in the art to make and use the claimed invention for the following reasons:

(1) ***Nature of the Invention & Breadth of the Claims***

Claim 2 is drawn to method for diagnosing *any* disease in a female subject using *any* experimental sample derived from said subject comprising; selecting *any* reference samples of *any* known disease state that are matched to said experimental sample in reproductive

state wherein the reproductive state of the individual is determined by determining *any* menstrual state of the individual; comparing the expression profile of said experimental sample to the expression profiles of said reference samples to identify the reference sample that matches said experimental sample in gene expression; and diagnosing the experimental sample with the disease of the matching reference sample.

Claim 4 is drawn to a method to diagnose *any* physiological disorders in a female comprising: comparing a gene expression profile from *any* experimental sample to a gene expression profile that represents an average of a plurality of reference samples wherein all of the reference samples in the plurality are from individuals of matched menstrual state, and wherein each of the reference samples in the plurality has been diagnosed with the same physiological disorder and wherein the experimental sample is from an individual whose menstrual state is matched to the menstrual state of the reference samples; and diagnosing the experimental sample with the physiological disorder if the gene expression profile of the experimental sample is similar to the gene expression profile that represents an average of a plurality of reference samples.

Claim 5 is drawn to a method to identify *any* reproductive status of a sample derived from a female comprising; generating *any* expression profile from *any* experimental sample, and comparing said expression profile from the experimental sample to a plurality of expression profiles from samples of known reproductive state status; wherein the reproductive state of the individual is determined by determining *any* menstrual state of the individual; identifying said reproductive status of said sample of unknown origin by identifying an expression profile of determined reproductive status that is similar to the

expression profile from the experimental sample.

Claim 6 is drawn to a method to identify *any* markers of different reproductive states in women comprising: obtaining a first gene expression profile from *any* sample from a first reproductive state and a second gene expression profile from a sample from a second reproductive state, wherein the reproductive state of the individual is determined by determining *any* menstrual state of the individual; comparing the expression profiles from said first and second reproductive states; identifying genes that are differentially expressed in said first and second reproductive states; and identifying at least one gene that is differentially expressed between the first and second reproductive states as a marker of different reproductive states in women.

Thus, the claims are drawn to a large genus of possible diseases to be diagnosed, physiological disorders to be diagnosed, reproductive statuses to be identified, markers of different reproductive states, samples to be obtained and gene expression profiles to be obtained.

(2) ***Relative Skill of those in the Art, State of the Prior Art, Amount of Direction or Guidance Presented & Presence or Absence of Working Examples***

As stated above, the claims are broadly drawn to methods of diagnosing any disease or physiological disorder, identifying any reproductive status and markers of reproductive states. Thus, the claims encompass diagnosing a large plurality of possible diseases, disorders, statuses and markers for statuses. Additionally, the claims are broadly drawn to encompassing the expression profiles from a vast plurality of possible genes or proteins. However, the specification (and the art) only provides guidance for methods of detecting expression of specific

genes in the proliferative and secretory endometrium, and methods of detecting expression of specific genes in the endometrial cancers of adenocarcinoma and clear cell carcinoma (see examples 1-3 on pages 31-39, and discussion below). Therefore, the specification and the art fail to provide the requisite direction and guidance to accomplish the breadth of the instant claims. More specifically, the prior art and the instant invention fail to provide any guidance or direction on the plurality of other possible expression profiles, diseases, disorders, statuses and markers for status that are encompassed by the instant claims.

For example, the specification defines "disease state" as "any abnormal biological state of a cell" (page 6, lines 9-10), and defines "physiological state" as "any normal biological state of a cell or organism (page 5, lines 21-22), wherein it would seem that a "physiological disorder" would be a disorder of "any normal biological state of a cell or organism". These recitations, "disease state" and "physiological disorder", are very broad and encompass a large number of possible conditions in a wide range of possible conditions, such as breast cancer, atherosclerosis, lactic acid buildup, paralysis, AIDS, etc., wherein only adenocarcinoma and clear cell carcinoma have been taught. Accordingly, the instant claims are not commensurate in scope with its supporting disclosure.

Furthermore, neither the disclosure nor the art provides the necessary guidance and direction in actually carrying out the invention. All of the claims are directed to either determining the "menstrual state" or use "menstrual state" in accomplishing in their goals. However, the specification, nor the art, define "menstrual state", teach what is encompassed by this recitation, or teach how to determine "menstrual state". Furthermore, the specification does not provide any guidance or direction as to how to "match" samples by "menstrual state". With

respect to claims 4 and 5, the specification does not provide any guidance as to what degree of similarity is required for determining whether the experimental sample can be diagnosed with the physiological disorder (or can be used to identify reproductive status). With respect to Claim 6, the specification does not provide guidance on the correlation and/or relationship between the differential expression of at least one gene and different reproductive states. Finally, it is noted that the specification does not actually carry out any of the method steps by example.

The specification does provide the following relevant working examples:

Example 1 teaches the detection of genes differentially expressed in the secretory and proliferative stage endometrium (see pages 31-36). Specifically, Table 1 shows genes downregulated in proliferative vs. secretory endometrium, and Table 2 shows genes upregulated in proliferative vs. secretory endometrium. However, these tables do not show a correlation or relationship between the expression profiles of the proliferative and secretory endometrium and any disease or physiological disorder.

Example 2 teaches various gene expression profiles (see pages 37-38). The tissues used in the study "were 4 'matched' adenocarcinomas, surgically obtained with 'matching' normal tissue" (see page 37). It appears as if the diseased and normal samples were obtained from the same tissue (e.g., a disease sample and a normal sample of a subject's endometrium was taken), however, due to the ambiguity of the term "matched", Applicants' clarification is respectfully requested. Table 5 shows "Genes differentially expressed in endometrial tumors", wherein 5 genes are present in tumors and absent in normals. Table 6 shows "Genes differentially expressed by at least 4 fold in endometrial tumors". However, despite the expression profiles presented, this example makes no mention of "menstrual state", "reproductive state" or

"reproductive status", and therefore it is not apparent how the expression profiles presented are related and/or are commensurate in scope to the claims. That is, Example 2 appears to teach the comparison of expression profiles of certain genes in normal samples and adenocarcinoma samples from the same subject, but does not provide any teachings regarding "menstrual state", how to determine "menstrual state", etc.

Example 3 teaches the differential expression in endometrial cancers (see page 39). Here, "matched" normal tissue and adenocarcinoma or clear cell carcinomas ranging from Grade I to III were collected from more than 10 patients. The data in Table 7 shows:

MIF and Cyclin A1 were not expressed in normal tissue, but were expressed in adenocarcinoma-diseased tissue.

HRG1 and HOX1 were expressed in normal tissue, but were not expressed in adenocarcinoma-diseased tissue.

Alpha 2 collagen type VI and Adducin are expressed in normal tissue, and were expressed in adenocarcinoma-diseased tissue, but lower than the normal. Adducin was expressed in clear cell carcinoma-diseased tissue, but lower than the normal.

Cyclin B and PKC zeta were expressed in adenocarcinoma-diseased tissue, and were expressed in the normal tissue, but lower than the diseased tissue.

Caplonin and Caldesmon were expressed in normal tissue, but were not expressed in clear cell carcinoma-diseased tissue.

Kertain K17, ESE-1b and HMG1 were not expressed in normal tissue, but were expressed in clear cell carcinoma-diseased tissue.

LAMB3, Laminin SB3 and Osteopontin were expressed in clear cell carcinoma-diseased tissue, and were expressed in the normal tissue, but lower than the diseased tissue.

Decorin was expressed in normal tissue, and was expressed in clear cell carcinoma-diseased tissue, but lower than the normal.

However, like Example 2, this example makes no mention of "menstrual state", "reproductive state" or "reproductive status", and therefore it is not apparent how the expression profiles presented are related and/or are commensurate in scope to the claims. That is, Example 3 appears to teach the comparison of expression profiles of certain genes in normal samples and adenocarcinoma samples from the same subject, but does not provide any teachings regarding "menstrual state", how to determine "menstrual state", etc.

Accordingly, while providing guidance for methods of detecting expression of specific genes in the proliferative and secretory endometrium, and methods of detecting expression of specific genes in the endometrial cancers of adenocarcinoma and clear cell carcinoma, neither the specification, nor the prior art provides the necessary guidance or direction to carry out the instant claims.

(3) ***Quantity of Experimentation Necessary & the Unpredictability of the Art***

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. In *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of

ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art.

In order to carry out making and using of the instant invention, the experimentation required by the skilled artisan would be considered undue. The skilled artisan would have to experiment to determine "menstrual states", "reproductive states", "reproductive statuses", "markers of different reproductive states", expression profiles of "disease states", expression profiles of "physiological disorders", expression profiles of "reproductive status", expression profiles of "reproductive state", and the diagnosis of "physiological disorders". Once the skilled artisan obtained expression profiles, the skilled artisan would have to test the expression profiles to determine whether the profiles are specific to particular "disease states", "physiological disorders", "reproductive status" and "reproductive state". Such experimentation requires a large amount of trial and error analysis, with little to no starting point, absent any teaching in the specification (see above), wherein the results of such analysis are unpredictable, and is therefore considered undue.

In essence, the experimentation that one skilled in the art would be required to perform is in fact the proposed novelty of the invention. However, "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". (*Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001).

Accordingly, in view of the unpredictability in the art and in view of the lack of specific disclosure in the specification, undue experimentation would be required to practice the invention as it is claimed.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 2 and 5 are rejected under 35 U.S.C. 102(a) as being anticipated by Srinivasan et al. (Clinical Cancer Research (1999) 5: 2877-2883).

Due to the ambiguity of the claims (see 112, 2nd paragraph rejections above), the recitations of "menstrual state", "reproductive state" and "reproductive status" have been interpreted broadly.

With respect to claims 2 and 5, Srinivasan teaches a method for diagnosing any disease (e.g., endometrial cancer), or reproductive status, in a female subject using an experimental sample derived from said subject comprising; selecting a reference sample of a known disease state (or reproductive status) that are matched to said experimental sample in reproductive state wherein the reproductive state of the individual is determined by determining the menstrual state (e.g., proliferative, secretory and hyperplastic stages) of the individual; comparing the expression profile of said experimental sample to the expression profiles of said reference samples to identify the reference sample that matches said experimental sample in gene expression; and diagnosing the experimental sample with the disease of the matching reference sample (or

identifying the reproductive status of the unknown, experimental status). (See abstract, pages 2878-2879 and 2881-2882).

10. Claims 2 and 4-6 are rejected under 35 U.S.C. 102(e) as being anticipated by Baban et al. (Pub. No. US 2002/0127555).

Due to the ambiguity of the claims (see 112, 2nd paragraph rejections above), the recitations of "menstrual state", "reproductive state" and "reproductive status" have been interpreted broadly.

With respect to claims 2 and 5, Baban teaches a method for diagnosing any disease (e.g., endometriosis), or reproductive status (e.g., likelihood of infertility), in a female subject using an experimental sample derived from said subject comprising; selecting a reference sample of a known disease state (or reproductive status) that are matched to said experimental sample in reproductive state wherein the reproductive state of the individual is determined by determining the menstrual state (e.g., proliferative or secretory and hyperplastic phases) of the individual; comparing the expression profile of said experimental sample to the expression profiles of said reference samples to identify the reference sample that matches said experimental sample in gene expression; and diagnosing the experimental sample with the disease of the matching reference sample (or identifying the reproductive status of the unknown, experimental status). (See abstract and page 1, paragraph 5; pages 2, paragraphs 15-17, 20-54, 66-68, 72-73, 75-76, 78-132, 148, 150, 164-179, Examples 1-2, Tables 1 and 3-11, and Claims 1-39, 43 and 48).

With respect to Claim 4, Baban teaches a method to diagnose a physiological disorders in a female comprising: comparing a gene expression profile from a experimental sample to a gene expression profile that represents an average of a plurality of reference samples wherein all of

the reference samples in the plurality are from individuals of matched menstrual state, and wherein each of the reference samples in the plurality has been diagnosed with the same physiological disorder and wherein the experimental sample is from an individual whose menstrual state is matched to the menstrual state of the reference samples; and diagnosing the experimental sample with the physiological disorder if the gene expression profile of the experimental sample is similar to the gene expression profile that represents an average of a plurality of reference samples. (See abstract and page 1, paragraph 5; pages 2, paragraphs 15-17, 20-54, 66-68, 72-73, 75-76, 78-132, 148, 150, 164-179, Examples 1-2, Tables 1 and 3-11, and Claims 1-39, 43 and 48).

With respect to Claim 6, Baban teaches a method to identify markers of different reproductive states in women comprising: obtaining a first gene expression profile from a sample from a first reproductive state and a second gene expression profile from a sample from a second reproductive state, wherein the reproductive state of the individual is determined by determining *any* menstrual state of the individual; comparing the expression profiles from said first and second reproductive states; identifying genes that are differentially expressed in said first and second reproductive states; and identifying at least one gene that is differentially expressed between the first and second reproductive states as a marker of different reproductive states in women. (See abstract and page 1, paragraph 5; pages 2, paragraphs 15-17, 20-54, 66-68, 72-73, 75-76, 78-132, 148, 150, 164-179, Examples 1-2, Tables 1 and 3-11, and Claims 1-39, 43 and 48).

11. Claims 2, 5 and 6 are rejected under 35 U.S.C. 102(e) as being anticipated by Nowak et al. (USPN 6,440,445)

Due to the ambiguity of the claims (see 112, 2nd paragraph rejections above), the recitations of "menstrual state", "reproductive state" and "reproductive status" have been interpreted broadly.

With respect to claims 2 and 5, Nowak teaches a method for diagnosing any disease (e.g., leiomyomas), or reproductive status, in a female subject using an experimental sample derived from said subject comprising; selecting a reference sample of a known disease state (or reproductive status) that are matched to said experimental sample in reproductive state wherein the reproductive state of the individual is determined by determining the menstrual state (e.g., proliferative and secretory stages) of the individual; comparing the expression profile of said experimental sample to the expression profiles of said reference samples to identify the reference sample that matches said experimental sample in gene expression; and diagnosing the experimental sample with the disease of the matching reference sample (or identifying the reproductive status of the unknown, experimental status). (See Figures 2-4 and cols. 4, 12 and 13).

With respect to Claim 6 Nowak teaches a method to identify markers of different reproductive states in women comprising: obtaining a first gene expression profile from a sample from a first reproductive state and a second gene expression profile from a sample from a second reproductive state, wherein the reproductive state of the individual is determined by determining *any* menstrual state of the individual; comparing the expression profiles from said first and second reproductive states; identifying genes that are differentially expressed in said first and second reproductive states; and identifying at least one gene that is differentially expressed

between the first and second reproductive states as a marker of different reproductive states in women. (See Figures 2-4 and cols. 4, 12 and 13).

12. Claims 2 and 5 are rejected under 35 U.S.C. 102(e) as being anticipated by Lessey, B. (USPN 5,854,401)

Due to the ambiguity of the claims (see 112, 2nd paragraph rejections above), the recitations of "menstrual state", "reproductive state" and "reproductive status" have been interpreted broadly.

With respect to claims 2 and 5, Lessey teaches a method for diagnosing a disease (e.g., infertility), or reproductive status, in a female subject using an experimental sample derived from said subject comprising; selecting a reference sample of a known disease state (or reproductive status) that are matched to said experimental sample in reproductive state wherein the reproductive state of the individual is determined by determining the menstrual state (e.g., proliferative and secretory stages) of the individual; comparing the expression profile of said experimental sample to the expression profiles of said reference samples to identify the reference sample that matches said experimental sample in gene expression; and diagnosing the experimental sample with the disease of the matching reference sample (or identifying the reproductive status of the unknown, experimental status). (See Figures 1-6 and cols. 2-6, 8, 10 and Table 10).

Conclusion

13. No Claims are allowable.

14. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Mutter, G. (Pub. No. US2002/0106662).

Abu-Jawdeh et al. (Laboratory Investigation (1999) 79(4): 439-447).

Florio et al. (Human Reproduction (1998) 13(9): 2606-2611).

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (571) 272-0788. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (571) 272-0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Alexander H. Spiegler
March 17, 2004

JEFFREY SIEW
PRIMARY EXAMINER
3/17/04